United States Environmental Protection Agency

LABORATORY ANIMAL PROJECT REVIEW

Please note:

1. All information in this LAPR is considered privileged and confidential by the IACUC and regulatory authorities.
2. Approved LAPRs are subject to release to the public under the Freedom of Information Act (FOIA). Do not include proprietary or classified information in the LAPR.
3. An approved LAPR is valid for three years.

LAPR Information

LAPR Title:	The identification of adverse outcome pathways for chemicals that affect neuroendocrine target sites involved with pubertal development in the rat.
LAPR Number:	18-03-001
Principal Investigator	Exemption 6
Author of this Document:	Exemption 6 RTP/USEPA/US
Date Originated:	03/02/2015
LAPR Expiration Date:	03/31/2018
Agenda Date:	03/11/2015
Date Approved:	03/20/2015
Date Closed:	

APPROVALS

APPROVER	NAME	APPROVAL DATE	COMMENTS	
	Exemption 6 RTP/USEPA/US by Exemption 6 /RTP/USEPA/US	03/20/2015	DMR	
	Exemption 6 Exemption 6 Exemption 6 /RTP/USEPA/US by Exemption 6 /RTP/USEPA/US	03/20/2015	DMR	

Administrative Information

1. Project Title (no abbreviations, include species):
The identification of adverse outcome pathways for chemicals that affect neuroendocrine target sites involved with pubertal development in the rat.

Is this a continuing study with a previously approved LAPR?
No

2. Programatic Information

a. What Program does this LAPR support? Please provide the Research Program, Project, Task Number and Title.
Research Program: Chemical Safety for Sustainability (CSS)
Project: Adverse Outcome Pathway Discovery and Development
Task Title: Development of AOPs for Reproduction in Vertebrates
Task Number: 1.3.b

b. What is the Quality Assurance Project Plan (QAPP) covering this project?
IRP-NHEERL-RTP/TAD/ETB[redacted]/2013-001-r000

3. EPA Principal Investigator/Responsible Employee:

Principal Investigator	*Phone Number*	*Division*	*Mail Drop*
Exemption 6	Exemption 6	TAD	MD
	Lotus Notes Address	*Branch*	B105-04
	[redacted] RTP/USEPA/US	ETB	

4. Alternate Contact:

Alternate Contact	*Phone Number*	*Division*	*Mail Drop*
Exemption 6	Exemption 6	TAD	MD
	Lotus Notes Address	*Branch*	B105-04
	[redacted]/RTP/USEPA/US	ETB	

SECTION A - Description of Project

1. Explain the study objective(s) in <u>non-technical language</u> such that it is understandable by non-scientific persons. <u>Explain how the benefits from the knowledge gained from this research outweigh the costs to the animals used in this research.</u> If this is a continuing study from a previous LAPR, briefly justify the continuation. Please spell out all acronyms and abbreviations with their initial use.

The main objective of this study is to identify adverse outcome pathways (AOPs), which are essentially cause-and-effect flowcharts that link chemicals with adverse biological outcomes, such as a disease state or alteration in development. AOPs start with an effect on a cellular process by a chemical (also known as a perturbation of a molecular initiating event), which leads to a cascade of biological changes ending in an adverse condition or state. The identification and understanding of AOPs are ultimately important for the interpretation of high-throughput data and its use in risk assessment.

The goal of our laboratory is to identify and to assist in mapping AOPs regarding pubertal development. We will use chemicals to alter specific neuroendocrine targets that are important during puberty. More specifically, we are going to examine chemicals that potentially disrupt hypothalamic neuronal signaling, such as those that may act by altering steroid synthesis, neurotransmitter synthesis, or by disrupting neurotransmitter receptor binding sites. Data collected will be used to link the effects of chemicals on these targets to adverse biological outcomes, such as altered pubertal onset or reproductive system development. Making linkages, such as these, is the cornerstone of the AOP approach.

Our final objective is to take data collected in vivo and use it to accurately verify current high-throughput in vitro assay data and/or to find suitable in vitro models/assays that produce results predictive of rodent model AOPs. Therefore, for the initial in vivo studies, we will be examining the effects of compounds that are known to act at specific neuroendocrine target sites. In both the male and female rat, we will examine compounds that may affect the progression of puberty by: induction of progesterone production (atrazine), cyclooxygenase-2 (COX-2) inhibition (celecoxib), alpha-adrenergic receptor binding disruption (amitraz), and dopamine-beta-hydroxylase inhibition (sodium dimethyldithiocarbamate). Studies have shown that these cellular processes in the brain are affected by the chemicals listed in parentheses. Although these chemicals have known effects on hypothalamic physiology, only atrazine has thus far been shown to affect puberty in the rat. Therefore, dose-response studies with these example compounds will provide valuable information about their exposure during the juvenile period and their effect on pubertal onset and/or reproductive system development. Once these in vivo effects are established, we can then help verify current high-throughput data and/or develop testing strategies for evaluating the potential neuroendocrine targets in vitro. Thus, the knowledge gained by the use of animals in this project may facilitate fewer animals to be used in future studies, which is beneficial in a plethora of ways.

2. Scientific rationale for proposed animal use.

a. Why is the use of animals necessary?

The use of animals is necessary for development and validation of AOPs as only an animal model provides the complex interactions of the neuroendocrine system within an intact animal. In vitro test systems used to evaluate linkages along proposed AOPs must ultimately be compared against data from intact animal models.

b. Justify the species requested:

The rat is the species of choice because there is a high degree of conservation between the human and the rat in the neuroendocrine regulation of puberty, including the pathways and targets of interest for this study. Furthermore, the rat is specified in the EPA Endocrine Disruptors Screening and Testing Program and has commonly been utilized as a model species for hormonal and neuroendocrine system studies and, thus, there is an abundant amount of literature that we can utilize as a valuable resource and potentially contribute towards.

3. How was it determined that this study is not unnecessary duplication?

While previous studies have characterized disruption of hypothalamic neuronal signaling, very few appear to have investigated the effect of chemicals on the specific targets of interest (listed in A1) and link them to AOPs of pubertal and reproductive system development. We have extensively searched PubMed with terms associated with the effects of progesterone production induction, COX-2 inhibition, alpha-adrenergic receptor binding disruption, and dopamine-beta-hydroxylase inhibition with regards to pubertal and reproductive system development. However, we have not found any studies that utilize AOP approaches in linking neuroendocrine targets to adverse health effects for the ultimate purpose of making quantitative predictions.

SECTION B - In Vivo Procedures

1. Briefly describe the experimental design. Include descriptions of the age, weight and sex of the animals. Supplementary information may be attached at the end of the LAPR, but please include critical information within the body of the LAPR.

To control for postnatal day (PND), we will order time-pregnant dams from Charles River and have the litters born on-site. Time-pregnant dams will arrive on gestational day (GD) 13 and day of birth (DOB) will be designated PND0. On PND1, litter sizes will be assessed and pup sex determinations will be made. On PND20, pups will be weighed, weaned and randomized across treatment groups.

To ensure dosing over the pubertal developmental timeframe, female rats will be dosed once daily for approximately 20 days starting on PND21, while male rats will be dosed once daily approximately 30 days starting on PND23. These exposure timeframes are in conjunction with what is accepted for the male and female pubertal assays of the US EPA Endocrine Disruptor Screening Program (EDSP). Body weight will be measured once daily for all animals during the entire dosing period.

To evaluate pubertal development, females will be observed for vaginal opening (VO) starting on PND26, while males will be assessed for preputial separation (PPS) beginning on PND36. These daily observations will be made until maturity has been reached. Once females have reached maturity (the day of VO), they will be assessed for estrous cyclicity via vaginal lavage.

On the final day of dosing, animals will ultimately be euthanized via decapitation and trunk blood will be collected for serum and components of the reproductive system will be analyzed (weights, collected for histology, etc.).

2. Justify the number of animals. Include explanation (e.g., biological, statistical, regulatory rationale) for the number of animals needed for each treatment group, and the overall number requested for the duration of the LAPR.

Based on our previous experience with studies of pubertal exposure and altered neuroendocrine effects in the developmental animal, we propose that we will need 12 pups of each sex per treatment to obtain the number of animals necessary at each time point to achieve statistical significance. For each chemical to be tested, we estimate that we would need 3 dosage groups and 1 control group. Therefore, we would need 24 (12 males and 12 females) per dosage group, which would equate to 96 pups per chemical (n = 4 dosage groups including control x 24 animals total). If we test 4 chemicals, then we would need approximately 384 pups (n= 4 x 96). For the number of pregnant dams, we will assume that each will give birth to 8 pups (4 male and 4 female) to be certain that we will have enough males and females for this study and to account for factors such as uneven sex distribution of litters and possibly small litter sizes. Therefore, if we need 192 males and 192 females for this study, we should be able to achieve that number with 48 pregnant dams assuming, on average, litters consist of 4 males and 4 females In entirety, we will need 48 dams and 384 pups for the successful completion of this project. However, due to factors such as uneven sex ratios, small litter size, unexpected litter loss, we will increase these numbers to 60 adult animals and 480 offspring to ensure we have enough animals to complete this study.

3. State how many animals over the study period are expected to be used under the following three categories of pain/distress (USDA nomenclature as defined in the instructions): Please enter numbers only.

Categories	*Adults*	*Offspring*
C) Minimal, transient, or no pain/distress:	60	480
D) Potential pain/distress relieved by appropriate measures:		
E) Unrelieved pain/distress:		

4. Does this LAPR include any of the following:

☐ Restraint (>15 Minutes) ☐ Survival surgery

☐ Food and/or water restriction (>6 Hours) ☐ Non-survival surgery

5. Category C procedures. Describe each procedure separately, include details on the following:

a. Treatments (e.g., dosages, duration of exposure, route, volume, frequency):

Experimental chemicals will be dissolved in corn oil and the dosing volumes will be based on rat body weight. Dosing solutions for oral gavage will be prepared so that the animal receives 5mL of solution per kilogram body weight. For example, if a 250g (i.e., 0.250kg) rat were to be dosed with sodium dimethyldithiocarbamate at 6.25mg/kg, 6.25mg sodium dimethyldithiocarbamate would be dissolved in 5mL of corn oil, and the rat would be dosed with 1.25mL of 6.25mg sodium dimethyldithiocarbamate/5mL corn oil solution.

For juvenile rats, dosing solutions will be administered orally via 20 gauge steel feeding needles where dosing volumes will be determined as described above. We estimate that juveniles may weigh from 50-300 g during the pubertal developmental timeframe (dependent on PND and sex), and dosing volumes per rat will range from 0.25mL to 1.5mL per day.

For this study, dosing will include:

Test Agent	Doses	Target
Atrazine	0 – 50mg/kg/day	Progesterone production inducer
Celecoxib	0 – 20mg/kg/day	COX-2 inhibitor
Sodium dimethyldithiocarbamate	0 - 25 mg/kg/day	Dopamine-beta-hydroxylase inhibitor
Amitraz	0-100mg/kg/day	alpha-adrenergic receptor agonist

b. Survival Blood Collections (method, volume, frequency):

c. Testing methods (including non-stressful dietary restrictions/modifications, mild non-damaging electric shock):

At the time of weaning, male and female pups will be separately housed two per cage with one animal ear punched in order to differentiate the animals.

Pubertal endpoint assessment of male preputial separation (PPS) and female vaginal opening (VO) will require gentle handling and manipulation of animal genitalia, which has been done successfully in our laboratory without being stressful or painful to the animal.

Vaginal smears obtained via vaginal lavage after VO will be utilized to confirm estrous cyclicity for a period of two weeks. This procedure has also been performed successfully in our laboratory without being stressful or painful to the animal.

d. Animal restraint and confinement beyond routine housing and handling. Include a description of the type of restraint device, acclimation to device, duration of restraint:

e. Breeding for experimental purposes (e.g. length of pairing, number of generations):

f. Describe how animals will be identified and monitored. Include description of identification procedures. (For example, if transponders are used, how are the animals prepared?) Include frequency of observations and by whom:

Animals will be monitored daily and body weights will be measured throughout the treatment timeframe by the technical staff of Exemption 6Exemption 6Exemption 6 For animals receiving COX-2 inhibitor, Exemption 6 technical staff will be informed to closely monitor for signs of gastrointestinal bleeding and/or renal damage. This would be apparent for rats that suffer extreme weight loss and/or dehydration.

6. Non-surgical Category D or E procedures. Describe each procedure separately, include details on the following (Also fill in Section B.9).

a. Treatments (e.g. dosages, duration of exposure, route, volume, frequency):

b. Blood Collection (Provide a description of the procedure including method, volume, and frequency if appropriate. Indicate if the procedure is survival or terminal. Include preparatory methods, descriptions of incisions, etc.):

c. Testing methods:

d. Restrictions placed on the animals' basic needs (e.g., food and/or water restriction, light cycles, temperature). Provide details regarding the length of restriction. Describe the method(s) for assessing the health and well-being of the animals during restriction. (Amount of food or fluid earned during testing and amount freely given must be recorded and assessed to assure proper nutrition.):

e. Describe how animals will be monitored (e.g., frequency of observations, by whom):

f. Analgesia (Category D Procedures) - list drugs, dosages, route of administration and frequency:

g. If treatment-related deaths are expected, this must be thoroughly justified. Death as an endpoint is highly discouraged:

7. Surgical Category D and E procedures. Indicate if the surgery is survival or terminal. Describe each surgical procedure separately, include details on the following (Also fill in Section B.9)

a. Complete description of surgical procedure including presurgical preparation, aseptic technique, surgical closure, etc:

b. Anesthetic regimen (Drugs, dosages, volume, route of administration and delivery schedule). The use of paralytic or neuromuscular blocking agents w/o anesthesia is prohibited:

c. Postoperative care (thermal support, special feeding, responsible personnel, removal of sutures/staples, frequency and duration of monitoring including weekend and holiday care):

d. Post operative analgesics (drugs, dosage, and volume and route of administration, frequency):

e. Will any animal be subject to more than one surgical procedure over the course of its lifetime, either here at NHEERL or elsewhere?

◯ Yes ◯ No

f. Identify any surgical procedures performed at other institutions or by vendors:

8. Humane interventions (for treatments/procedures in all categories).

a. What resultant effects, if any, do the investigators expect to see following procedures or treatment? Please include transitory as well as permanent effects. Examples might include lethargy, ataxia, salivation or tremors. Indicate the expected duration of these effects.

If any animals appear to be sick by displaying signs of systemic toxicity, appear to have increased stress, and/or are not eating, then they will be promptly removed from the study and immediately euthanized. The attending veterinarian will be consulted when appropriate to determine the appropriate course of action.

Symptoms of toxicity:
Amitraz: coolness to touch, reduced spontaneous activity, periods of increased induced activity such as aggression in response to handling, and/or signs of general debilitation.

Atrazine: abdominal pain, diarrhea, eye irritation, irritation of mucous membranes, and possible skin reactions.

Celecoxib: gastrointestinal effects, may be an eye and skin irritant.

Sodium dimethyldithiocarbamate: gastrointestinal irritation with nausea, diarrhea; respiratory tract, skin, and eye irritation

There will be signage in the animal room alerting veterinary staff of potential effects of these chemicals when in use.

b. State the criteria for determining temporary or permanent removal of animals from the study. Describe actions to be taken in the event of deleterious effects from procedures or chemical exposures. Describe actions to be taken in the event of clinical health problems not caused by procedures or exposures.

Animals will be removed from the study if they show deteriorating body condition (Ullman-Cullere 1999, attached), excessive salivation, diarrhea, lethargy, and/or other signs of illness.

9. Alternatives to pain and distress (Category D and E Procedures only). Provide narrative regarding the sources consulted to ascertain whether acceptable alternatives exist for potentially painful/distressful procedures. Include databases searched or other sources consulted, the date of the search and years covered by the search, and key words and/or search strategy used. Assistance with searches is available through the EPA Library Staff.

SECTION C - Animal requirements

Describe the following animal requirements :

1. Indicate the number of animals required over the study period for this protocol. Please enter numbers only.

a. Animals to be purchased from a Vendor for this study:	60
b. Animals to be transferred from another LAPR:	
LAPR Number that is the source of this transfer:	
c. Animals to be transferred from another source:	
d. Offspring produced onsite (used for data collection and/or weaned):	480
e. TOTAL NUMBER of animals for duration of the LAPR	540

2. Species (limited to one per LAPR): Rat(s)

3. Strain: Wistar rats, Long Evans rats

Describe special requirements for animals with altered physiological responses (e.g., genetically altered, aged)

4. Sources of animals:

Charles River Laboratories

5. Provide room numbers where various procedures will be performed on animals:

Exemption 6

6. Will any animals be housed in areas other than the animal facility longer than 12 hours? If so, state location. Such areas require prior IACUC approval as a satellite facility before LAPR can be reviewed.

No *Room Numbers:*

7. Describe any transportation and containment methods involved in moving animals between EPA buildings, or between EPA and other institutions (excluding any commercial shipments)

N/A

8. Describe any unusual housing or husbandry requirements, or acclimation requirements.

Justify any treatment beginning less than 3 days after arrival.
N/A

9. Describe special assistance requested of the animal contract staff, including procedures and dosing. NOTE, this request must be submitted separately to the Animal Resources Program Office (ARPO)
We may need assistance from animal contract staff with dosing, body weight measurements, and smears via vaginal lavage.

10. Housing and Enrichment.
The IACUC encourages the use of environmental enrichment whenever possible (see IACUC website for details). Provide details on how the animals will be housed, including type of cage (e.g., solid bottom or wire screen), bedding material, number of animals per cage, and environmental enrichment. Note that housing rodents individually without environmental enrichment requires justification.
We request that polycarbonate cages with heat-treated pine shavings be used, where dams will be housed one per cage and weanlings will be housed two per cage. Our study will require that only pine shavings be used to prevent potential endocrine disruptor exposure from alternative bedding material.

SECTION D - Agents Administered to Animals

1. Identify all hazardous and non-hazardous agents to be administered to living animals. For agents requiring a Health and Safety Research Protocol (HSRP), provide the title of the approved HSRP for each such agent. If no protocol is required for an agent deemed potentially hazardous (e.g. nanoparticles, recombinant DNA), describe the safety precautions to be used.
Provide maximum dosing levels and route-appropriate LD50s (where available) for each agent used for dosing.

Test Agent	Maximum dosage	Oral rat LD50
Atrazine	50mg/kg/day	672mg/kg
Celecoxib	20mg/kg/day	>2000mg/kg
Amitraz	100mg/kg/day	523-800mg/kg
Sodium dimethyldithiocarbamate	25 mg/kg/day	1000 mg/kg
Corn oil (vehicle)	4.5g/kg/day	>90g/kg

Atrazine, celecoxib, and amitraz are included in HSRP 805: The evaluation of chemicals on the hypothalamic-pituitary-gonadal (HPG) axis and development.

2. Describe compounds to be administered to animals.
a. Are all substances pharmaceutical grade? If not, provide a scientific justification for the use of non pharmaceutical grade compounds.
All substances will be of highest grade readily available. Atrazine is a herbicide and sodium dimethyldithiocarbamate is a fungicide; these chemicals are not available in pharmaceutical grade. Celecoxib is a pharmaceutical COX-2 inhibitor and amitraz is available and used in veterinary applications; however, because the pharmaceutical formulations of these chemicals are inappropriate for this research, we will use the highest grade readily available for research use.

Additionally, the corn oil vehicle will be of food grade and used within 1 year of opening.
b. Describe any plans to administer human or animal tissues, blood or body fluids to the animals in the LAPR. Provide information to assure that such material is pathogen free. Indicate what safety precautions are necessary for handling the material.
N/A
c. Provide a statement regarding any safety precautions necessary for handling any of these materials.
N/A

NOTE: Any unresolved health/safety questions which arise during IACUC review of this LAPR will require consultation with the Safety, Health, and Environmental Management Office.

SECTION E - Personnel Training and Experience

1. Identify all project personnel conducting animal experimentation. Specify the techniques for which they have responsibility, and their relevant training and experience. Additional personnel may be added to the table below as a group (by Division) for Category C procedures. By so doing you are giving assurance that these personnel have received all required training and are qualified to perform the Category C techniques requested.

Use this area to type in additional personnel information not available in the table drop-down lists:

Hint: *The names in the first 2 lines of the table below are filled automatically from the Principal Investigator & Alternate Contact fields. A new line will be made available when a name is selected & upon leaving the name field (i.e. tabbing or clicking in another field).*

NAME	ROLE	SPECIFIC RESPONSIBILITY	RELEVANT TRAINING
Exemption 6	Principal Investigator	Develop study and assist with organization or any animal handling necessary.	Over 25 years of animal handling and performing research studies for endocrine studies. Has had all NHEERL-required training.
Exemption 6	Technical Staff	Develop and organize study, prepare doses, dose, monitor animals, and necropsy.	Over 5 years of animal handling and research study execution. Has had all NHEERL-required training.
Exemption 6	Technical Staff	Develop and organize study, prepare doses, dose, monitor animals, and necropsy.	Over 15 years of animal handling and research study execution. Has had all NHEERL-required training.
RTP-NHEERL	Tech Support	Category C Procedures	All NHEERL required training is complete.

SECTION F - Animal Breeding Colonies

This section pertains to the breeding of animals for maintenance of ongoing animal colonies. Do not include breeding that is part of experimentation and accountable under Section C.

Describe:

1. Estimated number of breeding pairs and liveborn per year

2. Breeding protocols and recordkeeping

3. Methods for monitoring genetic stability

4. Disposition of all offspring and retired breeders that are not used in accordance with the procedures described in this LAPR

SECTION G - Euthanasia

1. When will the animals be euthanized relative to experimental procedures?

Dams that birthed the pups for this study will be euthanized by Animal Care Staff shortly after the pups have been weaned.

Experimental animals will be euthanized on the last day of dosing. Approximately PND53 for male rats and PND41 for female rats.

2. Describe the euthanasia techniques:

Method(s): Decapitation without anesthesia
Agent(s):
Dose (mg/kg):
Volume:
Route:

Source(s) of information used to select the above agents/methods:

2013 AVMA Guidelines on Euthanasia., Personal Experience
Regarding decapitation, an alternate guillotine will be readily available when animals are to be sacrificed. Also, all staff that perform this method of euthanasia are highly experienced with this procedure.

3. Provide justification and references for any euthanasia agent or method that is not consistent with recommendations of the American Veterinary Medical Association (AVMA) Guidelines for Euthanasia (e.g., cervical dislocation or decapitation without anesthesia; cervical dislocation in rodents weighing more than 200 grams).

Decapitation without anesthesia is compliant with 2013 AVMA Guidelines for Euthanasia.

4. Describe how death is to be confirmed.

Prolonged absence of breathing

SECTION H - Disposition of Used and Unused Animals

Describe the disposition of any animals remaining after project completion.

Euthanized by Animal Care Contractor

The IACUC encourages investigators to reduce the overall number of animals used at NHEERL. Would you consider transferring any unused animals from this LAPR to another approved LAPR?

● Yes ○ No

SECTION I - Assurances

1. Animals will not be used in any manner beyond that described in this application without first obtaining formal approval of the IACUC.
2. All individuals involved in this project have access to this application, are aware of all EPA policies on animal care and use, and are appropriately trained and qualified to perform the techniques described.
3. Thorough consideration of the three "R"'s (Replacement, Reduction, Refinement) has been given, as applicable, to a. the use of animals, and b. procedures causing pain or distress (with or without analgesia/anesthesia), including death as an endpoint. The minimum number of animals required to obtain valid experimental results will be used.
4. The Attending Veterinarian has been consulted in regard to any planned experimentation involving pain or distress to animals.
5. The IACUC and Attending Veterinarian will be promptly notified of any unexpected study results that impact the animals' well-being, including morbidity, mortality and any occurrences of clinical symptoms which may cause pain or indicate distress.

6. All procedures involving hazardous agents will be conducted in accordance with practices approved by the Safety, Health, and Environmental Management Office.
7. I certify that I am familiar with and will comply with all pertinent institutional, state and federal rules and policies.
8. The IACUC has oversight responsibilities for animal care and use, and may request consultation or feedback regarding the conduct of in vivo procedures, progress and accomplishments, and any problems encountered.

EPA Principal Investigator	Certification Signature Date
Exemption 6 Exemption 6	03/04/2015

Submitted: 03/04/2015

Certification:

Certification by EPA Supervisor (Branch Chief or Division Director) that the project described herein has been reviewed and approved on the basis of scientific merit:

Branch Chief/Division Director	*Approval Date*	*Phone Number*	*Division*	*Mail Drop*
Exemption 6	03/04/2015 by Exemption 6 Exemption 6 Exemption 6 Exemption 6 Exemption 6 TP/USEPA/US	Exemption 6 *Lotus Notes Address* Exemption 6 Exemption 6 Exemption 6 Exemption 6 Exemption 6 /RTP/USEPA/US	TAD *Branch* RTB	MD *Submitted to Branch Chief for Approval* 03/04/2015 04:29 PM

ATTACHMENTS

18-03-001 PI resp 3-17-2015.pdf

Ullman-Cullere 1999 Body Condition Scoring A Rapid and Accurate Method for Assessing Health Status in Mice.pdf

Actions

First Update notification sent: 02/02/2016
Second Update notification sent:
First 2nd Annual notification sent:
01/31/2017
Second 2nd Annual notification sent:

1st Expiration notification sent: 02/02/2018
2nd Expiration notification sent: 03/02/2018

History Log: